Deoxygenations of Arene Oxides. Models for Enzymatic Deoxygenation

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The transfer of oxygen from arene oxides to nitrogen and sulfur-containing substrates is described and the possible biological significance relative to enzymatic deoxygenation discussed.

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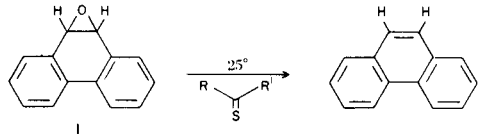
Sir:

Introduction

The recent recognition of the biological significance of arene oxides has generated an upsurge of interest in this unique class of compounds, particularly with respect to synthesis and biomechanistic pathways leading to aromatization, as well as nucleophilic ring-opening (1). Our interest in this area was kindled by the observation in our laboratories that K-region arene oxides undergo a general photorearrangement ("oxygen walk") (2) and that the deoxygenation of other *vic*-diaryloxiranes occurs upon photoexcitation (3). Transfer of oxygen from pyridine *N*-oxide to naphthalene has been reported by Jerina and co-workers, but this type of reaction also requires photoexcitation of the oxide (4). Trivalent phosphorus reagents are known to deoxygenate oxiranes to alkenes in a ground state reaction (5a) although elevated temperatures (~ 200°) are often required (5b). Recently, deoxygenation was found to occur in the ground state when benzene oxide was treated with isothiocyanate ion (6). In this case presumably arene sulfide formation occurs initially followed by thermal loss of sulfur with accompanying aromatization.

Results and Discussion

In the course of our investigations on 9,10-dihydro-9,10-epoxyphenanthrene (I), we have discovered an unusually facile and potentially significant deoxygenation process in which I is converted to phenanthrene upon treatment with thione reagents such as thiourea, *N*-methylbenzothiazole-2-thione, thioacetamide and thiosemicarbazone in organic solvents (benzene or methanol) at room temperature in the absence of added acid or base. In a typical case, 0.25 mmole of I and 1.0 mmole of thiourea were suspended in methanol (5 ml.) and stirred for 24 hours at ambient temperature. Subsequently, ether was added and the reaction mixture was washed with water



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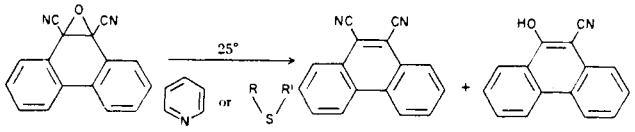
to separate the residual thiourea and other soluble by-products. After removal of volatile solvents from the organic phase, 42 mg. of a solid remained which consisted primarily of phenanthrene identified by mixture-melting point as well as mass spectral, infrared and tlc analyses.

Certain of the aforementioned thione reagents are known to react with oxiranes to give thiiranes (7); however, generally acid catalysis is required to achieve C-O bond cleavage. Determination of the mechanism of this deoxygenation process, and the structures of other minor, albeit potentially significant by-products, remain to be established as does the fate of the oxygen atom of I. It should be noted that the thione moiety appears to be required for deoxygenation since neither 2-mercaptobenzothiazole nor thiophene proved effective with respect to reduction of I. The facile thione-induced deoxygenation reaction of arene oxides appears to be general in character since both 4,5-dihydro-4,5-epoxypyrene and 9,10-dimethyl-9,10-epoxyphenanthrene (5b,8) are converted to their parent aromatic hydrocarbons (> 90%) under similar conditions. In fact, thiones may prove to be more practical reagents than phosphites and phosphines which are commonly used for deoxygenation in the structural elucidation of arene oxides.

The substituted phenanthrene oxide, 9,10-dicyano-9,10-epoxyphenanthrene (II) (9) is especially interesting for it displays a particularly high propensity to undergo reaction and transfers oxygen to an even broader spectrum of sulfur- and even nitrogen-containing compounds. For example, II interacts rapidly with pyridine at room temperature to give a deep bright red colored solution. The color gradually darkens upon standing (24 hours)

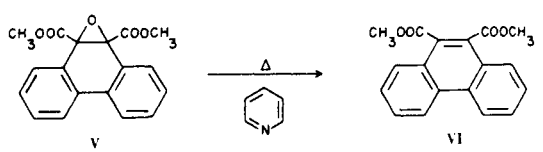
with concomitant formation of 9,10-dicyanophenanthrene III (13%) which was characterized by comparison of its infrared spectrum with that of an authentic sample (10). In addition, 10-cyano-9-phenanthrol (IV) (36%) and a dimer of IV (43%) (yet to be characterized) are also produced. The structure of the latter compound IV was assigned on the basis of combustion, infrared, and mass spectral analyses as well as the similarity of its ultraviolet spectrum to that of III. Methylation of the acidic



phenanthrol IV with diazomethane was also acheived to give the corresponding methyl ether whose spectral data are consistent with the proposed structure. It is of interest that the highly hindered 2,6-di-*t*-butylpyridine (Chemical Samples Co., Columbus, Ohio) gives no color formation or reaction with II even upon heating for prolonged periods.

In addition to pyridine, thiols, thioethers, and thiones react in a similar manner to give III and IV. In the case of the analogous 9,10-dicarbomethoxy-9,10-epoxyphenanthrene (V) (9) deoxygenation to 9,10-dicarbomethoxyphenanthrene (VI) is the only reaction observed although with pyridine it is necessary to heat the mixture (110°) overnight to observe the conversion. The diester VI was characterized by comparison with an authentic sample obtained from III and also by oxidation of 9,10-dimethylphenanthrene to the anhydride which in turn was converted to the dimethyl ester (11). Possibly V is less reactive than II in this regard because of steric factors or the lower electronegativity of the carbomethoxy group relative to the cyano group.

It is reasonable to assume in light of the results with V that the complex array of products observed in the case of II must arise as a result of the ability of the cyano group to undergo elimination as hydrogen cyanide in competition with water at an intermediate stage in the overall process. It is noteworthy in this connection that *trans*-dicyanostilbene oxide does not display any tendency to react under these ground state conditions.



Recently it was reported (12) that the reduction of arene oxides to the parent hydrocarbons (like oxidation of aromatics to their oxides) may be accomplished enzymatically. The relevant enzyme, designated as "epoxide reductase", was isolated in the microsomal fraction of rat liver. The ambient temperature photo- and ground state deoxygenations of I and II (as well as V) provide a mechanistic model for enzymatic reduction.

Further studies designed to define the scope and biosignificance of these findings are in progress and will be presented in detail in a subsequent full paper on this subject.

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